UTILITY PATENT APPLICATION TRANSMITTAL

(For new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. P30920C1

First Named Inventor or Application Identifier

John R. Dales

"EXPRESS MAIL CERTIFICATE"

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APPLICATION ELEMENTS *See MPEP chapter 600 concerning utility patent application contents.*	
1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to Deposit Account No. 19-2570 ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extensions of time, relating to this application. (37 CFR 1.136(a)(3)) *(Submit an original, and a duplicate for fee processing)*	7. ☒ The Title of the Invention: Preparation of Pruines 8. ☐ Nucleotide and/or Amino Acid Sequence Submission a. ☐ Computer Readable Copy b. ☐ Paper Copy (identical to computer copy) c. ☐ Statement verifying identity of above copies d. ☐ Use the identical computer-readable form filed in Application No. _____, filed ___as the computer-readable form for the instant application. (37 CFR 1.821(e))
2. ☒ The total fee is calculated as shown below: Basic Filing fee $760.00 Total Claims 13 - 20 = 0 x $18 $ 0.00 Independent Claims 3 -3 = 0 x $78 $ 0.00 ☐ Multiple Dependent Claim present. $260 TOTAL FILING FEE $760.00 ☒ Cancel in this application original claims 1 to 4 and 8 and 9 of the prior application before calculating the filing fee. ☒ Charge $760.00 to the above indicated Deposit Account.	ACCOMPANYING APPLICATION PARTS 9. a. ☐ Information Disclosure Statement (IDS) b. ☐ PTO-1449 c. ☐ Copies of all IDS Citations 10. ☐ Assignment Papers (cover sheet & document(s)) 11. ☒ Prior Application is Assigned to: SmithKline Beecham plc *(for continuation/divisional with Box 17a completed* 12. ☒ Preliminary Amendment [*Total Pages*] 6 13. ☒ Return Receipt Postcard (MPEP 503) *(Should be specifically itemized)*
3. ☒ Specification excluding Drawings [*Total Pages*] 11 4. ☐ Drawing(s) (35 USC 113) [*Total Sheets*] _____ 5. ☒ Declaration and Power of Attorney [*Total Pages*] 2 a. ☐ Newly executed (original or copy) b. ☒ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17a completed)* c. ☐ Unsigned Declaration *[Note Box 6 below]* i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).	14. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)* 15. ☒ Transfer all references cited by Applicants or by the Examiner from the parent Application Serial No. 08/732,479 filed October 18, 1996. A PTO-1449 listing the references is enclosed. 16. ☐ Other _____
6. ☒ Incorporation By Reference *(useable if Box 5b is checked)* The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 5b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.	

17. ☒ Priority Information, *check appropriate box and supply the requisite information*

a. The accompanying application is a ☒ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: 08/732,479 filed October 18, 1996.

b. ☐ Benefit is claimed under Title 35, United States Code, Section 119(e) of the following Provisional Applications: Application No. filed .

c. ☒ Please amend the specification by inserting before the first line the sentence: (37 CFR 1.78)
This is a continuation of application Serial No. 08/732,479 filed October 18, 1996 which is a 371 of International Application PCT/EP95/01840 filed April 19, 1995 which claims priority from GB9407698.1 filed April 19, 1994.

18. CORRESPONDENCE ADDRESS

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19. RESPECTFULLY SUBMITTED,

Signature _____

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EXPRESS MAIL LABEL NO.: EL175489903US

P30920C1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: John R. Dales
Predecessor Serial No.: 08/732,479
Filed: Herewith
For: Preparation of Purines

11 March 1999
Predecessor Art Unit No.: 1611
Predecessor Examiner: M. Berch

Assistant Commissioner of Patents
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination of the above noted application, entrance of the following remarks and amendments is respectfully requested.

In the Specification:

Page 1, under the title please amend the specification by adding the following:

-- Related Applications:

This application is a continuation of USSN 08/732,479 filed 18 October 1996 which is the §371 national stage entry of PCT/EP95/01840, filed April 19, 1995. –

In the Claims:

Please cancel Claims 1 to 4, 8 and 9.

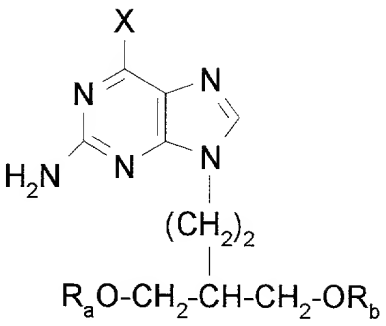
Please amend the following claims:

Claim 6, please change the claim dependency from "claim 1" to -- claim 10 --.

Claim 7, please change the claim dependency from "claim 1" to -- claim 10 --.

Please add the following claims:

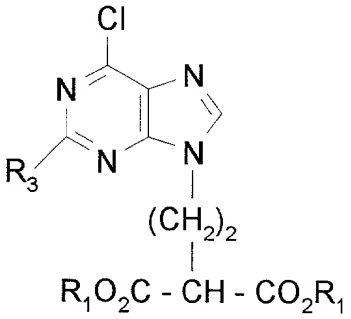
10. A process for the preparation of a compound of formula (A):



(A)

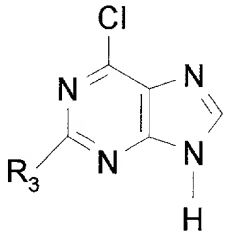
wherein:
X is hydrogen or hydroxy; and R_a and R_b are hydrogen or acetyl, which process comprises:

(i) the preparation of a compound of formula (I):



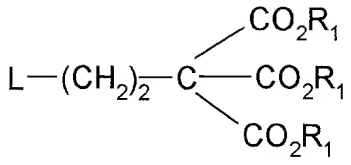
(I)

wherein R_1 is C_{1-6} alkyl, or phenyl C_{1-6} alkyl in which the phenyl group is optionally substituted; and R_3 is an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):



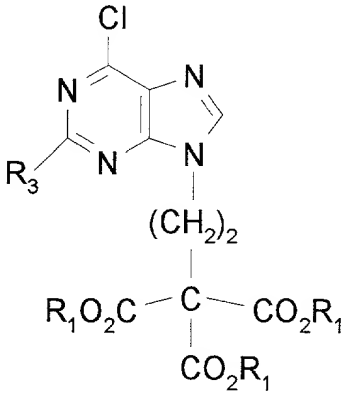
(II)

wherein R_3 is as defined above for formula (I), with a compound of formula (V):



(V)

wherein L is a leaving group and R_1 is as defined for formula (I), to give a compound of formula (VI):



(VI)

and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation; and

(ii) conversion of the resulting compound of formula (I) to a compound of formula (A) by:

a) removal, if necessary, of the amino protecting group;

b) reducing the ester groups CO_2R_1 to CH_2OH groups, and, if necessary, acetylating to form the corresponding CH_2OAc groups; and

c) dechlorinating via a hydrogenolysis reaction to yield a compound of Formula (A) in which X is hydrogen; or dechlorinating via a hydrolysis reaction to yield a compound of Formula (A) in which X is hydroxy.

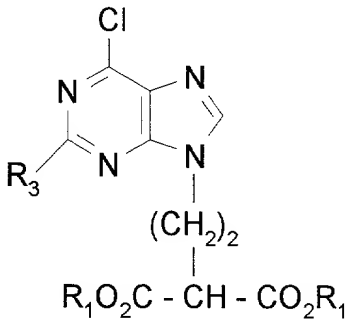
11. A process according to claim 10 wherein, in the compound of formula (V), R_1 is C_{1-6} alkyl and L is halogen.

12. A process according to claim 11, wherein L is bromo.

13. A process according to claim 10, wherein R_1 is methyl or ethyl.

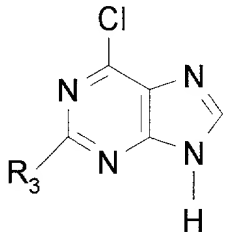
14. A process according to claim 10 wherein decarboxylation of the compound of formula (VI) is effected by the addition of about 0.42 equivalents of sodium methoxide.

15. A process for the preparation of a compound of formula (I):



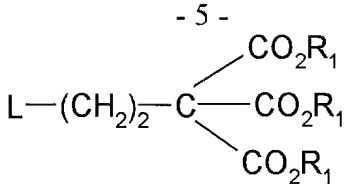
(I)

wherein R_1 is C_{1-6} alkyl, or phenyl C_{1-6} alkyl in which the phenyl group is optionally substituted; and R_3 is an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):



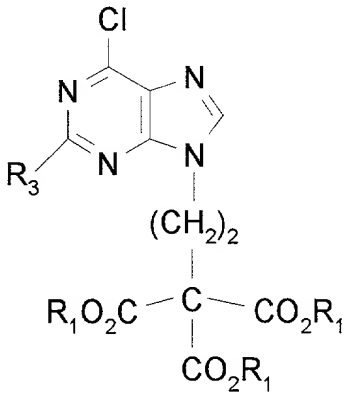
(II)

wherein R_3 is as defined for formula (I), with a compound of formula (V):



(V)

wherein L is a leaving group and R_1 is as defined for formula (I), to give a compound of formula (VI):



(VI)

and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation.

16. A process according to claim 15 wherein, in the compound of formula (V), R_1 is C_{1-6} alkyl and L is halogen.

17. A process according to claim 16, wherein L is bromo.

18. A process according to claim 15, wherein R_1 is methyl or ethyl.

19. A process according to claim 15 for the preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine.

20. A process according to claim 15 wherein decarboxylation of the compound of formula (VI) is effected by the addition of about 0.42 equivalents of sodium methoxide.

REMARKS

Claims 5 to 7 and 10 to 20 are in the application. Claims 1 to 4, 8 and 9 have been cancelled. Claim dependency of claims 6 and 7 has been changed. Claims 10 to 14 have been added. Support for the hydrogenolysis and hydrolysis language in Claim 10 finds support in EP 302644, page 7, line 55 and EP 141927, page 5, line 17 which are claimed in originally filed claims 8 and 9, and described in the specification on page 1, lines 6 to 29.

A copy of the Declaration of Grahm Richard Geen submitted in the parent application accompanies this amendment.

An Information Disclosure Statement and PTOL 1449 form also accompany this amendment. Applicants respectfully request that the references cited therein be transferred from the parent application (08/732,479) to this continuation application

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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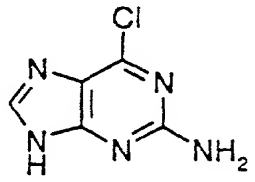
PREPARATION OF PURINES

This invention relates to a process for the preparation of pharmaceutical compounds.

The compound 2-amino-6-chloropurine (ACP) of formula:



is a useful intermediate in the preparation of nucleoside analogue antiviral agents, such as penciclovir (previously known as BRL 39123) and famciclovir (previously known as BRL 42810), described in EP-A-141927 (Example 1) and EP-A-182024 (Example 2), respectively. The intermediate is 9-substituted with an appropriate side chain precursor, followed by conversion of the 6-chloro moiety to a hydroxy (a guanine) or hydrogen (a 2-aminopurine).

A process from ACP is generally described in EP-A-302644 and US Patent No 5175288 and an improved process over the process specifically described in this publication has now been discovered. The key difference is that in the original process the chlorine group in the 6-position of the purine molecule is removed early in the process (see reaction Scheme 1). Significant yield and processing advantages are obtained by retaining the 6-chloro substituent in the molecule through the process, removing it only at the final step (see reaction Scheme 2). With streamlining of the process stages and removal of the column chromatography steps, which would have rendered the route disadvantageous as a production process, overall yields have been increased from 10.6% to 41%.

Accordingly, the present invention provides a process for the preparation of penciclovir/famciclovir from ACP which process comprises the process from ACP as described in EP-302644, characterised in that the 6-chloro substituent is removed subsequent to the decarboxylation and hydrolysis steps.

As no aqueous dilution is used to precipitate the product at the coupling step there is large capacity advantage, and the dimethylformamide is more easily recovered as it does not have to be separated from a large volume of water.

There are greater overall volume efficiencies in the process.

The following Examples illustrate the invention.

EXAMPLE 1

(Stage 1 Product)

Preparation of 2-amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl)purine

A mixture of 2-amino-6-chloropurine (9.18g, 53.1 mmole), triethyl 3-bromopropane-1,1,1-tricarboxylate (20.33g, 57.3 mmole), potassium carbonate (11.1g, 80.3 mmole) and dimethylformamide (190ml) were stirred together at 60°C to 63°C for 22h. After this time the reaction mixture was filtered hot through a celite bed and the cake washed with dimethylformamide (30ml). The filtrate and washing were combined and the solvent removed under high vacuum distillation to leave a crude reddish brown oil. This was dissolved in methanol (140ml), cooled to 20°C and then a solution of sodium methoxide (1.2g) in methanol (40ml) was added with stirring. After ca 20 minutes a precipitate formed and the stirring was continued for a total of 1 hour. The reaction mixture was then cooled to 15°C and held at this temperature for 30 minutes. The product was filtered off and washed with methanol (10ml) and dried at 40°C for 16h under vacuum.

Yield: 12.0g of 95% purity material.

EXAMPLE 2

(Stage 2 product)

Preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-chloropurine

A mixture of 2-amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl) purine (32.7g, 0.1 mole), sodium borohydride (11.5g, 0.3 mole) and methylene dichloride (125ml) were stirred at 20°C. Methanol (75ml) was added dropwise over 2.0 hour period while the reaction temperature was maintained at 20-22°C with cooling. The reaction mixture was left to stir for a further 1.5h. Water (100ml) was added followed by the dropwise addition of concentrated hydrochloric acid (20-22ml) to pH 6.7 to 7.0 keeping the reaction temperature at 20°-22°C. Methylene dichloride and methanol were removed under vacuum until a reaction volume of 150ml was obtained. The reaction mixture was cooled to 5°C and stirred at this temperature for 30 minutes. The resulting precipitate was filtered off and the product cake washed with cold water (20ml). The resulting damp solid (40-50g) was stirred with triethylamine (15ml), 4-dimethylaminopyridine (1.0g) in methylene dichloride (250ml). Acetic anhydride (75ml, 0.79 mole) was added dropwise over 20 to 30 minutes at such a rate to control the reflux. The reaction mixture was heated under reflux for a further 1.5 hours. The reaction was cooled to 20°C and neutralised with 20% w/w sodium hydroxide solution to pH 6.4-6.5. The methylene dichloride layer was separated and the aqueous phase extracted with methylene dichloride (100ml). The combined methylene dichloride phases were evaporated to dryness. The crude damp solid was recrystallised from 3:1 methanol:water (75ml), cooling the precipitate to -5°C for 1h before filtration. The product was washed with cold 3:1 methanol:water (0°C) and dried at 40°C for 16h in a vacuum oven.

Yield: 23g of 97% to 98% purity material

EXAMPLE 3

(Stage 3 Product)

a) Preparation of 9-(4-acetoxy-3-acetoxymethylbut-l-yl)-2-aminopurine - famciclovir

A mixture of 9-(4-acetoxy-3-acetoxymethylbut-l-yl)-2-amino-6-chloropurine (15.4g, 43 mmole), 5% palladium on carbon (6.16g), triethylamine (6.6ml, 47 mmole) and ethyl acetate (77ml) was stirred at 50°C under a hydrogen atmosphere at 1 bar pressure in an autoclave for 3 to 5 hours. After completion of the reaction the mixture was removed from the autoclave which was washed out with ethyl acetate (30ml) keeping the washings at 50°C. The main reaction mixture was filtered through a celite bed followed by the washings and finally with ethyl acetate (30ml). Water (46ml) was added to the combined ethyl acetate filtrate plus washings. The ethyl acetate was evaporated to dryness to leave a crude white solid. This was recrystallised from n-butanol (62ml), stirring the cooled solution at 0 to 5°C for 3h before filtration. The product was filtered off and washed with the mother liquors. The solid was reslurried in n-heptane (50ml) stirred for 30 minutes and filtered. The product was dried at 40°C for 16h under vacuum.

Yield: 11-11.3g

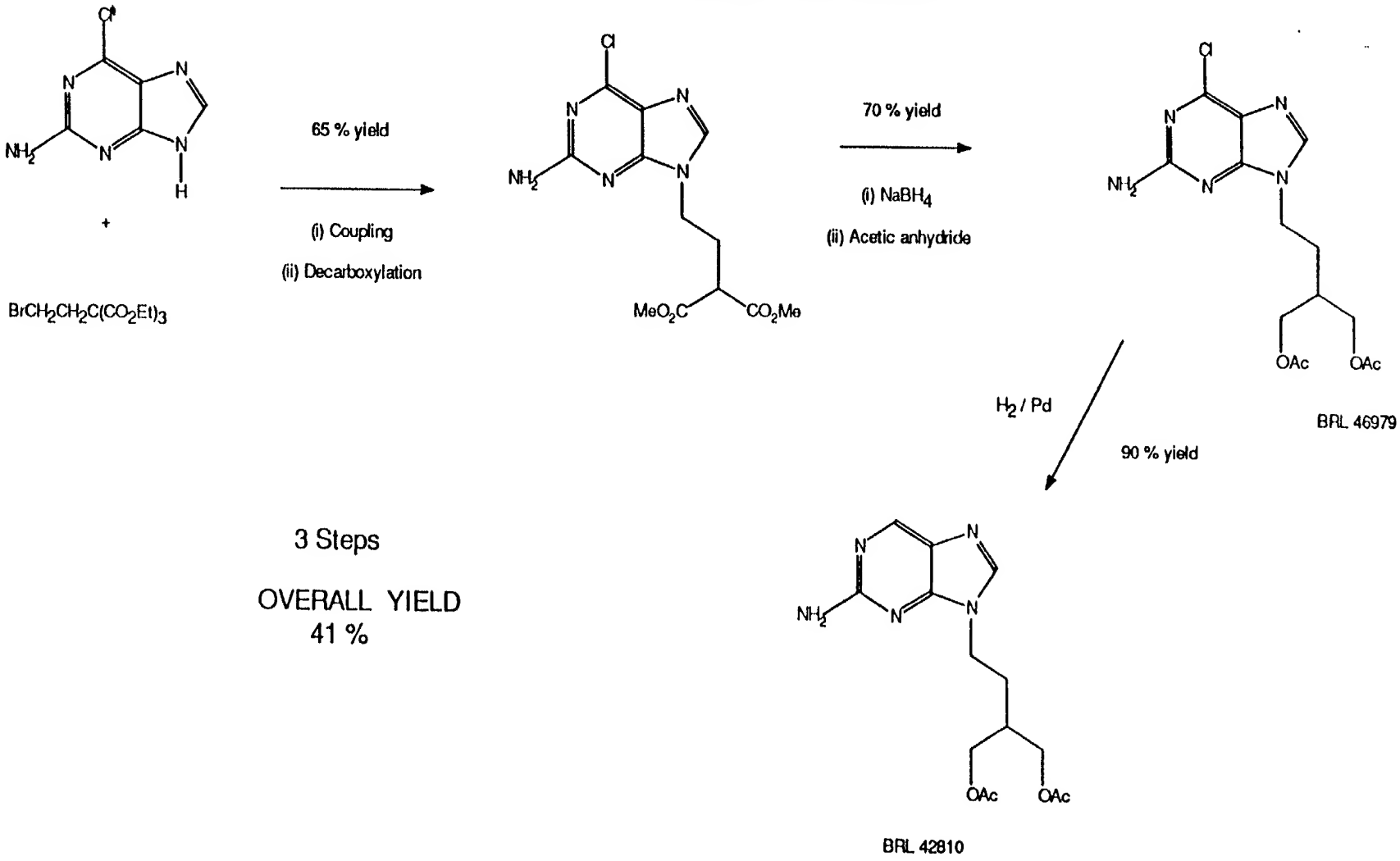
b) Preparation of 9-(4-hydroxy-3-hydroxymethylbut-l-yl) guanine - penciclovir

A mixture of 9-(4-acetoxy-3-acetoxymethylbut-l-yl)-2-amino-6-chloropurine (10g, 28.1mmole), formic acid (96%, 6.3ml) and water (55ml) was stirred and heated to reflux for about 4 hours. After cooling the solution was basified by mixing with sodium hydroxide solution (12.5M, 27ml) and the resulting solution was stirred for 1.5 hrs. The solution was neutralised by the addition of formic acid. The resultant slurry was heated to reflux (ca 105°C) then cooled to 40 - 45°C and stirred for about 3 hours. The crude product is then isolated and washed with water (20ml). The isolated product was dissolved in sodium hydroxide solution (3M, 80ml). Carbon (ca 1.5g) was added and the slurry stirred for about 1 hr then the carbon was removed by filtration and washed with water (20ml). The solution was neutralised by the addition of formic acid and the resultant precipitate was redissolved by heating to ca 100°C and was then cooled. The precipitated product was stirred for about 3 hrs then isolated and washed with water (2 x 20ml) before being dried.

Yield 5.3 - 5.5g.

Process of EP-A-302644
56 % total yield
(i) Coupling
(ii) Part Recrystallisation + Part Chromatography
95 % yield
H2 / Pd
59 % yield
(i) NaOEt
(ii) Column Chromatography
50 5 % yield
(i) NaBH4
(ii) Column Chromatography
67 % yield
Acetic anhydride
BrCH2CH2C(CO2Et)3
5 Steps
OVERALL YIELD
10.6 %
BRL 42810
(scheme 1)

Process of the Invention



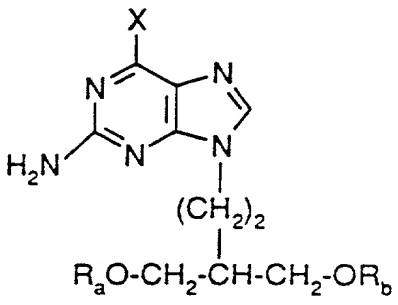
3 Steps

OVERALL YIELD
41 %

(scheme 2)

Claims

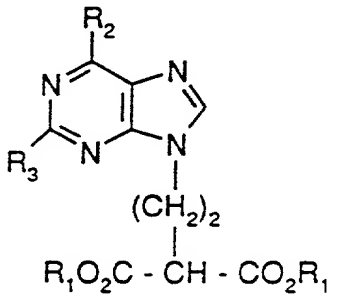
1. A process for the preparation of a compound of formula (A):



(A)

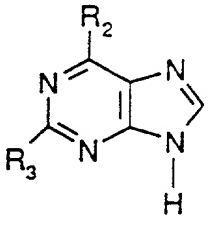
wherein:
X is hydrogen, hydroxy, chloro, C_{1-6} alkoxy or phenyl C_{1-6} alkoxy; and R_a and R_b are hydrogen, or acyl or phosphate derivatives thereof, which process comprises:

(i) the preparation of a compound of formula (I):



(I)

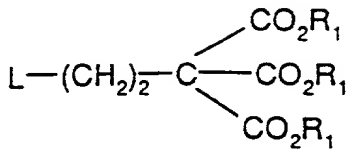
wherein R_1 is C_{1-6} alkyl, or phenyl C_{1-6} alkyl in which the phenyl group is optionally substituted; R_2 is hydrogen, hydroxy, chlorine, C_{1-6} alkoxy, phenyl C_{1-6} alkoxy or amino; and R_3 is halogen, C_{1-6} alkylthio, C_{1-6} alkylsulphonyl, azido, an amino group or a protected amino group, which preparation comprises the reaction of a compound of formula (II):



(II)

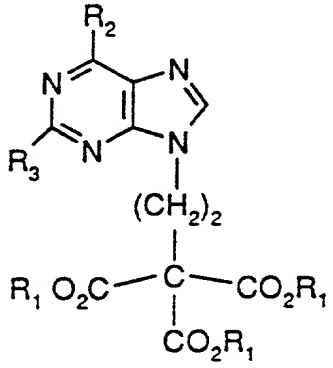
wherein R_2 and R_3 are as defined for formula (I) with:

a compound of formula (V):



(V)

wherein L is a leaving group and R_1 is as defined for formula (I), to give a compound of formula (VI):



(VI)

and thereafter converting the intermediate compound of formula (VI) to a compound of formula (I) via decarboxylation, and, as necessary or desired, interconverting variables R_1, R_2 and R_3 to further values of R_1, R_2 and R_3;

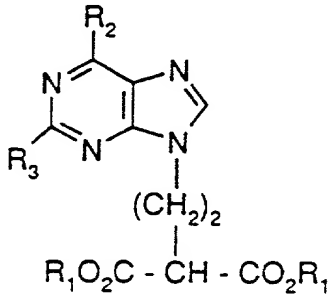
(ii) the conversion of the resulting compound of formula (I) to a compound of formula (A) by converting variable R_3, when other than amino, to amino, reducing the ester groups CO_2R_1 to CH_2OH and optionally forming acyl or phosphate derivatives thereof, and as necessary or desired converting variable R_2 in the compound of formula (I) to variable X in the compound of formula (A);

characterised in that

R_2 is chloro in formula (I).

2. A process for the preparation of a compound of formula (I) as defined in claim 1, which process comprises the reaction of a compound of formula (II) wherein R_2 and R_3 are as defined in claim 1 with a compound of formula (V) wherein R_1 is C_{1-4} alkyl and L is halogen, followed by decarboxylation of the resulting compound of formula (VI), and, as necessary or desired, interconverting R_1, R_2 and R_3 in the resulting compound of formula (I) to further values of R_1, R_2 and R_3 as defined for formula (I) in claim 1.

3. A compound of formula (I) wherein R_2 is chloro, or a salt thereof:



(I)

wherein R_1, R_2 and R_3 are as defined in claim 1.

4. A compound according to claim 3 or a salt thereof, wherein R_1 is methyl or ethyl and R_3 is amino.

5. 2-Amino-6-chloro-9-(methyl 2-carbomethoxybutanoate-4-yl)purine.

6. A process according to claim 1 for the preparation of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine (famciclovir).

7. A process according to claim 1 for the preparation of 9-(4-hydroxy-3-hydroxymethylbut-1-yl)guanine (penciclovir).

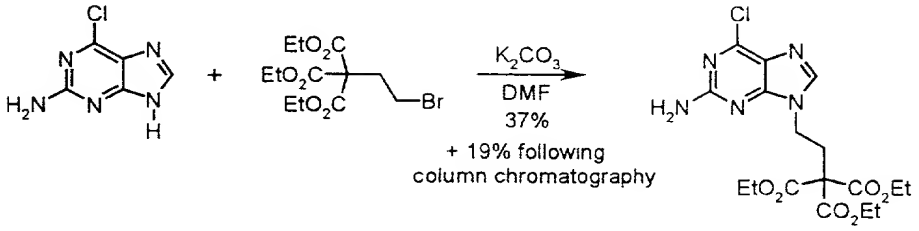
8. A process for the preparation of famciclovir from 2-amino-6-chloropurine (ACP) which process comprises the process from ACP as described in EP-A-302644, characterised in that the 6-chloro substituent is removed subsequent to the decarboxylation and hydrolysis steps.

9. A process for the preparation of penciclovir from 2-amino-6-chloropurine (ACP) which process comprises the process from ACP as described in EP-A-302644, characterised in that the 6-chloro substituent is removed subsequent to the decarboxylation and hydrolysis steps.

Annex 1

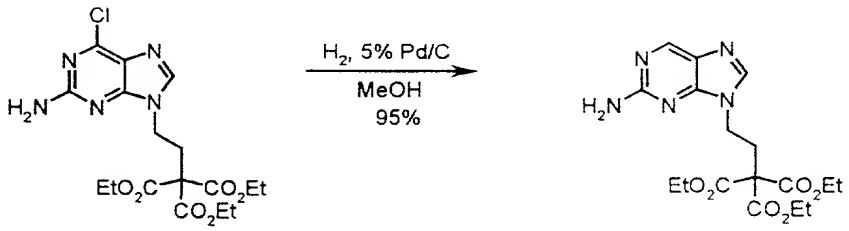
PROCESS FOR THE PREPARATION OF FAMVIR DISCLOSED IN EP 0 302 644 B1

Description 11

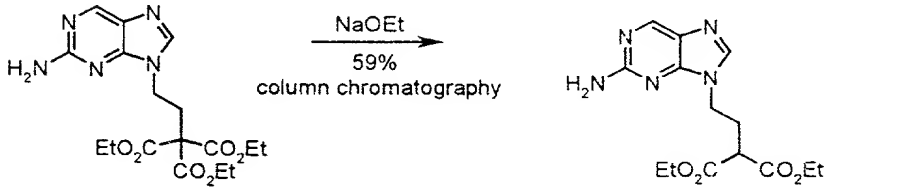


(reaction produces N-9 and N-7 triesters, plus smaller amounts of corresponding diesters)

Description 12

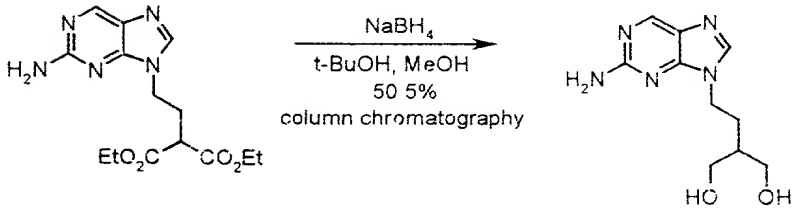


Example 3

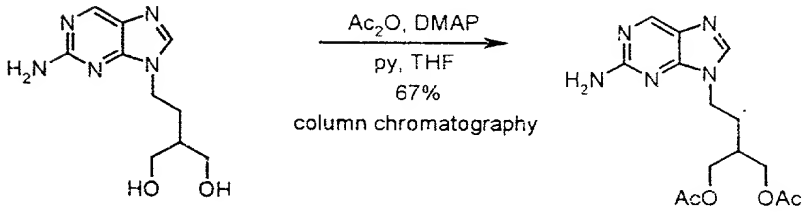


corresponding dimethyl ester is an oil
(see Example 1)

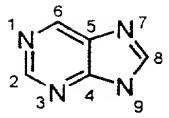
Preparation b) p.14

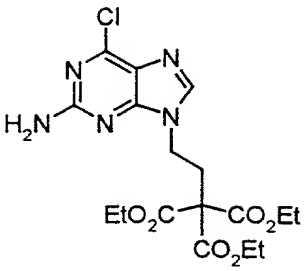


Preparation c) p.14

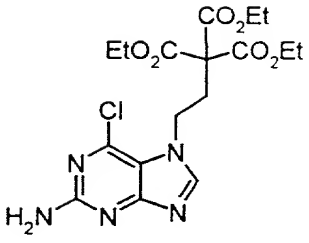


ANNEX 2

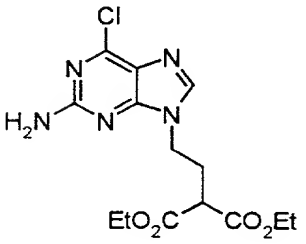




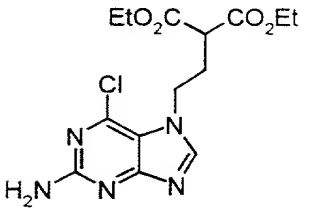
COMPOUND 1



COMPOUND 2



COMPOUND 3

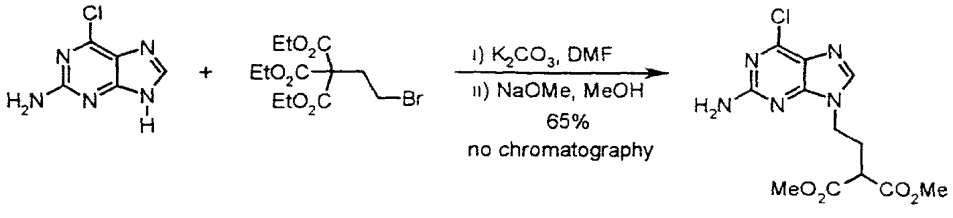


COMPOUND 4

ANNEX 3

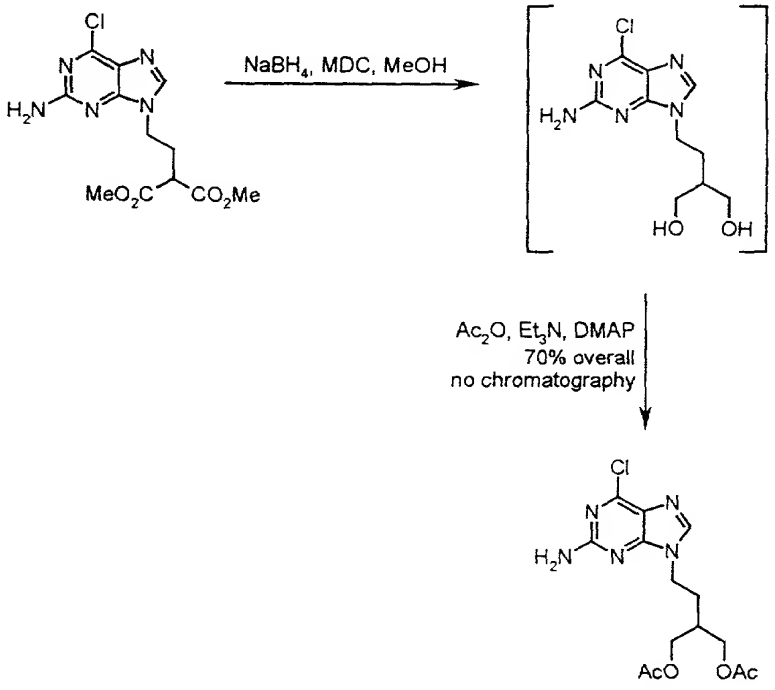
PROCESS FOR THE PRODUCTION OF FAMCICLOVIR DISCLOSED IN USSN 08/732,479

Example 1

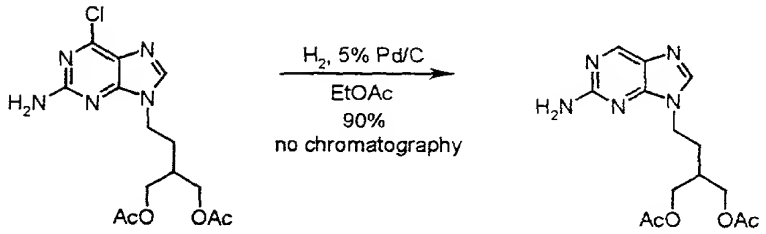


COMPOUND 5

Example 2



Example 3a



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Dales
Serial No:	08/732,479
For:	Preparation of Purines
Art Unit No..	1611
Examiner:	Mark L Berch

DECLARATION OF GRAHAM RICHARD GEEN

I, Graham Richard Geen, hereby declare

1. That I am Graham Richard Geen of SmithKline Beecham p.l.c., New Frontiers Science Park, Harlow, Essex, CM19 5AW, United Kingdom. I was awarded an honours degree of Bachelor of Science (Chemistry) in 1973 and the degree of Doctor of Philosophy in 1979, both from the University of Bristol. Since 1979 I have been employed by Beecham Group p.l.c. and SmithKline Beecham p.l.c. in various capacities relating to medicinal and synthetic chemistry, having spent 14 years working in the antiviral field. At the present time, I am an Assistant Director in the Department of Synthetic Chemistry. I am responsible for the work of 7 graduate chemists. I am an author or co-author of over 25 scientific publications and presentations

2. I am familiar with the present application US Serial No. 08/732,479 ('479), which relates to a process for the production of purines, e.g. famciclovir and penciclovir. I am also familiar with European Patent Application No. 302644 ('664) filed 25 July 1988, for which I am named as joint inventor.

3. '644 discloses a process for the production of purines of formula (A) using as starting materials a purine derivative of formula (II), e.g. 2-amino-6-chloropurine (ACP), and a tricarboxylate of formula (V). The desired compound of formula (A) does not contain a 6-chloro substituent, but a hydrogen. The process shown in '644 uses ACP as a starting material, but does not indicate when the chlorine should be removed to yield the desired dechlorinated final product of Formula (A). The only guidance regarding removal of the 6-chloro substituent in the '644 application is provided for in the

exemplified production of famciclovir. This process uses the following sequence of reactions, see Annex 1:

a) coupling of triethyl 3-bromopropane-1,1,1-tricarboxylate (formula (V)) to 2-amino-6-chloropurine (formula (II)) (Description 11),
b) removal of the 6-chloro substituent (R_2) (Description 12),
c) decarboxylation (Example 3);
d) reduction (Step A(b)); and
e) *O*-acetylation (Step A(c)).

4 The coupling step a) of '644 produces not only the desired N-9 isomer (Compound 1, Annex 2) and the unwanted N-7 isomer (Compound 2, Annex 2), but also smaller amounts of the corresponding N-9 and N-7 diesters (Compounds 3 and 4, Annex 2) which result from *in situ* decarboxylation. The process of '644 is inconvenient for use on a large, commercial scale, because it requires chromatographic separation of the desired N-9 isomer and unwanted N-7 isomer. In addition to suppressing the yield of the desired N-9 isomer (Compound 1, Annex 2, the presence of the N-9 and N-7 diesters (Compounds 3 and 4, Annex 2) further complicates the isolation of the N-9 isomer since 4 products are present in the reaction mixture. Hence in Description 11 the isolation procedure for Compound 1, Annex 2, involves numerous steps, viz:

i) removal of N,N-dimethylformamide;
ii) addition of ethyl acetate, washing and drying;
iii) removal of ethyl acetate;
iv) recrystallisation from butan-1-ol;
v) evaporation of butan-1-ol from filtrate;
vi) column chromatography of filtrate residue; and
vii) evaporation of eluant.

5. The process of '479, which was invented during attempts to facilitate large scale commercial production of purines of formula (A), uses the following sequence of reactions, see Annex 3:

a) coupling of compound of formula (V) with a compound of formula (II) to yield a compound of Formula (VI) (Example 1);
b) decarboxylation (Example 1) (to give Compound 5, Annex 3),
c) reduction (Example 2);
d) *O*-acetylation (Example 2); and
e) removal of the 6-chloro substituent (R_2) (Example 3)

Notably, in this process the 6-chloro substituent remains in place until the final step of the synthesis instead of being removed after the coupling step a) as in '644

6. In the process of '479 the triethyl ester (VI) is converted without isolation to the dimethyl ester, Formula (I), this N-9 isomer is then selectively precipitated from solution, free of the unwanted N-7 isomer. The process of '479 thus avoids the problems encountered in '644 since the presence of the 6-chloro substituent

allows the N-9 isomer to be selectively precipitated from the N-7 isomer, and decarboxylation of the entire reaction mixture reduces the number of products from 4 to 2. The advantage offered by this process is illustrated by the fact that the coupling and decarboxylation steps of the '479 process give an overall yield of 65% whereas the decarboxylation step alone of '644 only gives a yield of 59%.

7. In the process of '479 the yield at each step, and the overall yield, is substantially improved compared with that obtained using the process of '644 The overall yield of the '479 process is 41% and the overall yield of '644 process is 10 6% The improved yields of the present invention arise through the maintained presence of the 6-chloro substituent until the end of the synthesis.

8. A further advantage of the process of '479 is found in the reduction step, paragraph 5 (c) above, where the reaction mixture is worked up using an aqueous solvent In this step, it was found that the 6-chlorodiol is in fact less soluble than the dechlorinated diol, thus allowing easy isolation of the acetylated intermediate of the '479 process (see Example 2). This advantage is illustrated by the fact that the reduction and *O*-acetylation steps of the '479 process give a yield of 70% whereas the reduction and *O*-acetylation steps of the '644 process give a yield of 50.5% x 67% = 33.8%.

9. To summarize, the continued presence of the 6-chloro substituent during decarboxylation and through to the final step of the process is particularly advantageous because it allows:

a) convenient separation of the N-9 and N-7 isomers without requiring chromatography; and

b) the presence of the 6-chloro substituent in the diol produced in the reduction step decreases the solubility of the diol allowing convenient isolation in an aqueous solvent.

These advantages could not have been predicted from the disclosure of '644

10. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of this application or any patent issuing thereon.

Date: _____ _____

Docket No.: P30920 PCT/EP95/01840

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PREPARATION OF PURINES

the specification of which (check one)

[ ] is attached hereto.

[X] was filed on 19 April 1995 as Serial No. PCT/EP95/01840
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9407698.1	Great Britain	19 April 1994	Yes

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Stephen Venetianer	Registration No. 25,659
Stuart R. Suter	Registration No. 26,590
Janice E. Williams	Registration No. 27,142
James M. Kanagy	Registration No. 29,550
Edward T. Lentz	Registration No. 30,191
William T. King	Registration No. 30,954
Herbert H. Jervis	Registration No. 31,171
Linda E. Hall	Registration No. 31,763
Mary E. McCarthy	Registration No. 32,917
Charles M. Kinzig	Registration No. 33,252
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Yuriy P. Stercho	Registration No. 33,797
Kirk Baumeister	Registration No. 33,833
Wayne J. Dustman	Registration No. 33,870
Jeffrey A. Sutton	Registration No. 34,028
William T. Han	Registration No. 34,344
Nora Stein-Fernandez	Registration No. 36,689
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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of Inventor: John Robert Mansfield DALES

Inventor's Signature: J R M Dales Date: 3rd October 1996

Residence: Worthing, West Sussex, England

Citizenship: British

Post Office Address: SmithKline Beecham Corporation
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P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

United States Patent & Trademark Office

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Application deficiencies were found during scanning:

☐ Page(s)_____ of _____ were not present for scanning. (Document title)

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☐ Scanned copy is best available.

3 SHEETS of ANNEX BEGINS WITH Pg. number 4 TO 6

Only 10 sheets of Specification